REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following commentary.

I. Status of the Claims

Claims 8 and 12 were cancelled previously. Claims 35-37 are added with support in the original claims. Claim 1 has been amended with support in the original specification, for example, at page 9, penultimate paragraph. Claims 9, 20 and 28 have been amended to replace the trademark with its corresponding chemical name. Although withdrawn subject to a restriction requirement, claims 15, 23 and 31 have been amended with exemplary support in the specification, at page 18, second paragraph, and claims 22 and 30 have been amended for greater clarity. The Examiner is respectfully reminded that pursuant to MPEP 821.04, nonelected claims directed to a process of making and/or using the product may be rejoined for examination upon allowance of the product claims.

Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 1-7, 9-11, 13-14 and 35-37 will be under examination, with claims 15-34 withdrawn from consideration.

II. Statement of the Substance of the Interview

Applicants thank Examiner Mina Haghighatian for the courtesies extended during the interview with Applicants' representative, Christian Bauer, on April 16, 2008. The difference between the claimed invention and the cited art was discussed during the interview. Examiner Haghighatian's position is that both the composition of Wiedmann and the sterile filtration process of Desai are all well-known compositions/processes, and all that is claimed by the Applicants is a known process applied to a known composition. Examiner Haghighatian particularly relies on paragraph [0167] and Examples 8 and 9 of Desai in support of her

conclusion that it is well-known that one of ordinary skill in the art can sterile filter *any* composition containing drug particles having a size less than 200 nm by passing the composition through a filter having a pore size of 0.2 μm. Upon submission, Examiner Haghighatian will consider a response or declaration attesting to unexpected results.

III. Rejection of Claims under 35 U.S.C. §103(a)

A. Wiedmann and Desai

Claims 1-7, 9-11 and 13-14 are rejected under 35 U.S.C. §103(a) for alleged obviousness over U.S. Patent No. 5,747,001 to Wiedmann *et al.* ("Wiedmann") in view of U.S. Patent Application Publication No. 20070117862 by Desai *et al.* ("Desai"). Applicants respectfully traverse the rejection.

The Examiner's rejections relies on the conclusion that sterile filtration of solid dispersions of nanoparticles in a liquid medium is well-known in the art as taught by Desai. *See* Office Action, page 4, second full paragraph. Applicants respectfully disagree with this conclusion for at least two reasons. First, the Examiner overreaches in forming the conclusion from the teaching of Desai that sterile filtration of *all* solid dispersions of nanoparticles in liquid mediums is known in the art. Second, the Examiner has ignored the unpredictability of successfully sterile-filtering solid dispersions of nanoparticles in liquid mediums as shown in the Examples of Applicants' original specification.

1. The Examiner's conclusion from the teaching of Desai is overly broad.

In formulating the rejection, the Examiner relies on her conclusion that Desai teaches that *all* solid dispersions of nanoparticles in liquid mediums can be sterile filtered. In support of this broad conclusion, the Examiner relies on paragraph [0167] and Examples 8 and 9 of Desai. In contrast to the Examiner's conclusion, one of ordinary skill in the art would not read the limited

teachings in paragraph [0167] and Examples 8 and 9 of Desai as extending to *all* solid dispersions of nanoparticles in liquid mediums.

For example, paragraph [0167] is limited to a discussion of the supposed advantages of Desai's heavily proteinated drug particles having a size less than 200 nm. This paragraph states that the ability to sterile filter a composition having protein-rich particles is of great importance because one cannot sterilize such protein-rich particles by autoclaving. (Whether protein-rich particles can be sterile filtered and not autoclaved is not germane to the Examiner's conclusion drawn in the Office Action.) The proceeding paragraphs, [0168]-[0170], then explain how to make a protein-rich particles that can be sterile filtered. Paragraph [0168] begins by stating: "In order to obtain [these] sterile-filterable particles (i.e., particles <200 nm) . . ." Nothing in these paragraphs teach how to make particles of the present invention, or even that of Wiedmann. In fact, Desai distinguishes his protein-rich particles from "conventional" particles in paragraph [0168]. Accordingly, paragraph [0167] does not support the Examiner's broad conclusion that *all* solid dispersions of nanoparticles in liquid mediums can be sterile filtered.

Another example of how the Examiner's conclusion from her read of Desai is overreaching is the citations to Examples 8 and 9. Example 8 is limited to the drug isoreserpine, a paclitaxel, and human serum albumin as the protein. Example 9 does not exemplify another drug nor does it exemplify another protein. In fact, Example 9 is the same composition as Example 8: isoreserpine in combination with human serum albumin. Again, Examples 8 and 9 do not support the Examiner's broad conclusion that *all* solid dispersions of nanoparticles in liquid mediums can be sterile filtered.

2. The Examiner ignores Applicants' evidence of unpredictability.

Another reason that the Examiner's citation to the limited teachings of Desai does not support the conclusion that *all* solid dispersions of nanoparticles in liquid mediums can be sterile

filtered is the unpredictability of success evidenced by Applicants' own patent application specification.

The U.S. Supreme Court decision *KSR International Co. v. Teleflex Inc.* sets forth the examination guidelines for determining obviousness under 35 U.S.C. §103(a), applying the rationale of combining a known technique to a known device (method, or product) ready for improvement to yield predictable results. *See* the EXAMINATION GUIDELINES FOR DETERMINING OBVIOUSNESS UNDER 35 U.S.C. §103..., published in the *Federal Registrar*, Vol. 72, No. 195 (October 10, 2007), hereafter "the Guidelines."

Pursuant to the Guidelines, an examiner seeking to advance the combination rationale is obliged to articulate:

(1) a finding that the prior art contained a "base" device (method, or product) upon which the claimed invention can be seen as an "improvement;"

(2) a finding that the prior art contained a known technique that is applicable to the base device (method, or product);

(3) a finding that one of ordinary skill in the art would have recognized that applying the known technique would have yielded ***predictable*** results and resulted in an improved system; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

If any of these findings cannot be made, then this rationale is unavailable to validate a conclusion that the claim(s) in question would have been obvious, within the meaning of Section 103.

In the present instance, the Examiner has failed to meet the initial burden, pursuant to the Guideline requirements, of establishing a *prima facie* case of obviousness. This is so because, contrary to the Examiner's contention, combining the known technique of sterile filtration of

Desai[1] with the composition of Wiedmann would not have yielded the predictable results. This "unpredictability" is evidenced by the examples in the original specification. As such, Applicants do not believe that it is necessary to submit a declaration at this time, attesting to the facts clearly presented in the original specification.

For example, Examples 1 and 3 comprised budesonide and tyloxapol as a surface stabilizer. Effective average particles size was less than 150 nm. These compositions were successfully sterile filtered. Examples 2 and 4 comprised budesonide and tyloxapol plus an additional surface stabilizer (HPMC and PVP). The effective average particles size of these compositions was less than 150 nm. Now compare Examples 5-9. The active agent was budesonide, but the surface stabilizer was not tyloxapol. The effective average particle size of these compositions were less than 200 nm (expect for Example 7 – 276 nm and Example 9 – 203 nm). According to the Examiner's read of Desai, at least the compositions in Examples 5, 6, and 8 should have bene capable of sterilization by filtration. Surprisingly, they were not.

Now consider a different active agent, beclomethasome. Examples 11 comprised beclomethasome and tyloxapol as a surface stabilizer with an average particle size of less than 150 nm. This composition was sterile filterable. Example 10 comprised beclomethasome and tyloxapol plus an additional surface stabilizer. The effective average particle size was less than 150 nm and the composition was successfully sterilized by filtration. Examples 12 and 14 comprised beclomethasome with surface stabilizer of polysorbate 80 and PVP respectively. Both these compositions had an effective average particle sizes greater than 0.2 μm and were not successfully sterilized by filtration. The composition in Example 13 comprised beclomethsasome with polysorbate 20 and had an effective average particle size of less than 0.2 μm. However, this composition was not successfully sterilized.

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[1] In making this argument, Applicants will assume that, contrary to the evidence presented in Section 1. above, that one of ordinary skill in the art would read the teachings of Desai and conclude that *all* solid dispersions of nanoparticles in liquid mediums can be sterile filtered.

From Examples 1-14, one might conclude that the presence of tyloxapol determines whether a composition is successfully sterilized, assuming the effective average particle size was less than 0.2μm. Not so. Example 15 contained flunisolide with tyloxapol and had an effective average size of less than 0.2 μm. Suprisingly, Example 15 was not sterile filterable. Consider further Examples 16-18 which included triamcinalone with tyloxapol (either alone or in combination with another surface stabilizer). Examples 16-18 each had effective particle sizes under 0.2 μm, but were not successfully sterile filtered.

Accordingly, Applicants own specification provides evidence to the contrary that one of ordinary skill in the art would not have recognized that applying the Examiner's allegedly known technique (i.e., that *all* solid dispersions of nanoparticles in liquid mediums can be sterile filtered) would have yielded ***predictable*** results and resulted in an improved composition.

Because the Examiner has advanced no contravening evidence or compelling logic to support the proposition that any nanoparticulate beclomethasone/budesonide compositions comprising particles having an effective average particle size of less than 150 nm would have been able to pass through a filter with a pore size of 0.2 μm or less, the claimed invention is non-obvious over the cited art, and the subject rejection should be withdrawn.

B. Wood and Desai

Claims 1-7, 9-11 and 13-14 are rejected under 35 U.S.C. §103(a) for alleged obviousness over PCT Publication No. WO 96/25918 by Wood *et al.* ("Wood") in view of Desai. Applicants respectfully traverse the rejection.

The Examiner asserts that Wood, which allegedly teaches a dispersion comprising nanoparticulate beclomethasone particles having a particle size of less than 100 nm and a surface stabilizer, in combination with Desai, which allegedly teaches it is well-known that *all* solid dispersions of nanoparticles in liquid mediums can be sterile filtered, renders the claims obvious

because the claimed invention is applying a known technique to improve a known composition. Since the rationale for the rejection is similar to the rejection citing Wiedmann and Desai, Applicants' response to the rejection is the same as that in section III A.

IV. Discussion of the Teachings of Wiedmann and Westesen

In the Office Action dated June 7, 2007, the Examiner rejected claims 1-14 for alleged obviousness over Wiedmann in view of U.S. Patent No. 6,207,178 to Westesen et al. ("Westesen"). Applicants respectfully traverse the rejection.

The Examiner acknowledges that "Wiedmann lacks teachings on sterile filtration" (2007 Office Action, page 4, lines 1-2) but relies on Westesen's alleged teaching of sterile filtration to remedy the deficiency.

First, as discussed in the response filed on September 6, 2007, Westesen fails to disclose how dispersed particles are themselves incorporated into the solid lipid particles (SLPs). Rather, particles of the bioactive substance, if any, are formed as a result of the SLP formation process. *See* column 11, lines 5-60. More specifically, Westesen teaches that the bioactive substance and the SLPs are melted together (lines 16-20). After melting, the dispersion is filtered "***prior to cooling below the recrystallization temperature***" (lines 42-45, emphasis added). Westesen therefore infers that recrystallization of the dispersion may prevent filtration from being utilized as an effective means of sterilization.

Second, as demonstrated by the working examples in the original specification and submitted in the foregoing paragraphs, combining the sterile filtration technique of Westesen with the nanoparticulate dispersion of Wiedmann would not have produced predictable results, as required by the Examination Guidelines.

In view of the foregoing, the claimed invention is non-obvious over the cited art. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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